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Organo-Cation Catalyzed Asymmetric Homo/Hetero-Dialkylation of Bisoxindoles: Construction of Vicinal All-Carbon Quaternary Stereocenters and Total Synthesis of (–)-Chimonanthidine

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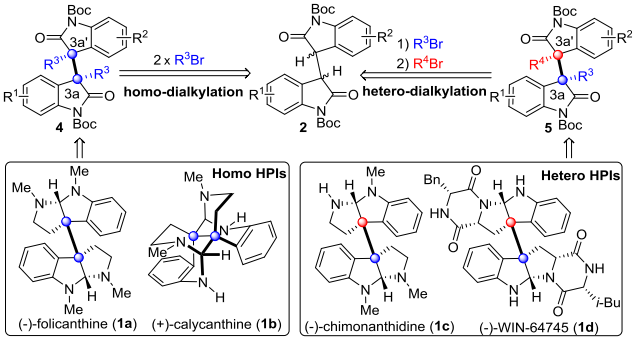
Supporting Information Placeholder

ABSTRACT: A novel chiral spirocyclic amide (SPA)-derived triazolium organocatalyst has been designed and demonstrated to effect asymmetric homo and hetero dialkylations of various bisoxindoles, enabling enantioselective construction of vicinal all-carbon quaternary stereocenters. These reactions feature excellent enantio- and diastereo-selectivities (up to 99% ee and >20:1 dr), as well as good to high yields (up to 89% over two steps). As an application of this methodology, the first asymmetric total synthesis of (–)-chimonanthidine has been achieved.

A large number of natural dimeric and oligomeric hexahydropyrroloindole (HPI) alkaloids (including homo- and hetero- types, Scheme 1) exhibit important biological activities, such as antifungal and cytostatic properties.[1] Structurally, these molecules usually incorporate a couple of sterically hindered vicinal all-carbon quaternary stereocenters at C_{3a} and $C_{3a'}$, which is regarded as "a daunting challenge" from an organic synthesis perspective.[2-7] In fact, the catalytic asymmetric construction of this congested motif is so difficult that only limited synthetic methodologies have been documented so far, namely, the double Michael addition[6c] and the double decarboxylative allylation.[6f,6i] Furthermore, these reported approaches do not always give both high yield and diastereoselectivity, and they are only applicable to synthesis of the homo-type alkaloids. As a result, there is a great need for a more efficient and versatile catalytic asymmetric dialkylation methodology (as illustrated in Scheme 1) to approach this motif.

In past decades, tetraammonium, triazolium salts and related organic cationic catalysts have been demonstrated to be powerful in the mono-alkylation of 2-oxindoles.[8,9] However, they have rarely been reported to enable the dialkylation of bisoxindole. A possible reason is due to the increased steric interaction between C_{3a} and $C_{3a'}$ during the second alkylation.[3] This interaction could lead to unexpected side reactions, such as diastereoisomeric alkylation and cleavage of the C_{3a}-$C_{3a'}$ bond, resulting in low stereoselectivity or chemical yield.[10] Another challenge facing this methodology is accessing the hetero-type of dialkylation (Scheme 1), which requires a good enough match of the reactivity and stereocontrollability of two different electrophiles (R^3Br and R^4Br). Therefore, design of a robust and effective catalytic system to address these challenges is crucial for facilitating this asymmetric

Scheme 1. Representative HPI alkaloids and our designed synthetic strategies

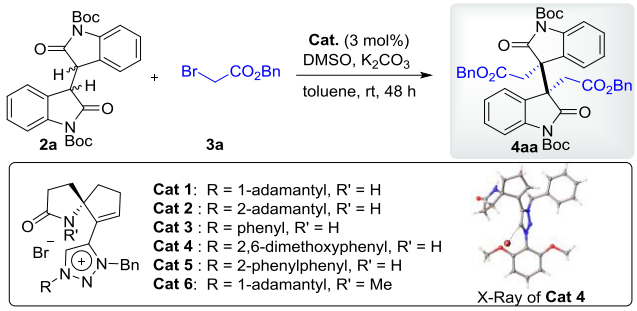


dialkylation. Based on our successful SPD (spirocyclic pyrrolidine) catalysis[11] together with a linear trazolium catalysis for mono-alkylation of 2-oxindoles.[8h,9b,9f,12] Herein, we describe a novel type of SPA (spirocyclic amide)-triazolium cationic catalyst, with which we have successfully carried out both homo- and hetero- asymmetric dialkylation of bisoxindoles and completed the first asymmetric total synthesis of natural (–)-chimonanthidine.

Our investigation began with the design and preparation of several novel SPA-triazolium bromide catalysts (**Cat 1**–**6**, Table 1), and we confirmed their absolute conformations by X-ray diffraction of **Cat 4**.[13] Bisoxindole **2a** and the commercially available benzyl bromoacetate **3a** were then selected as model substrates to investigate the organocatalytic asymmetric dialkylation. After extensive screening of various solvents, bases and additives,[13] the anticipated homo-dialkylated product **4aa** was obtained with a good result under the catalysis of 3 mol% **Cat 1** (entry 1, 74% yield, 93% ee, 12.6:1 dr). Although other catalysts (**Cat 2**–**6**) were also able to catalyze this reaction (entries 2–6), inferior results were generally obtained. Notably, the *N*-methyl substituted **Cat 6** gave the worst enantioselectivity (-6% ee, entry 6), indicating that the presence of the *N*-proton of SPA- type catalysts was essential for generation of stereoselection during this asymmetric reaction.

After establishing the optimal **Cat 1** and experimental procedure, we expanded electrophiles R^3Br toward the homo-dialkylation of **2a**. The results are listed in Table 2 and showed that three groups of electrophiles **I**–**III** (Group **I**: benzyl bromoacetate esters **3a**–**i**, Group **II**: alkyl bromoacetate esters **3j**–**l** and

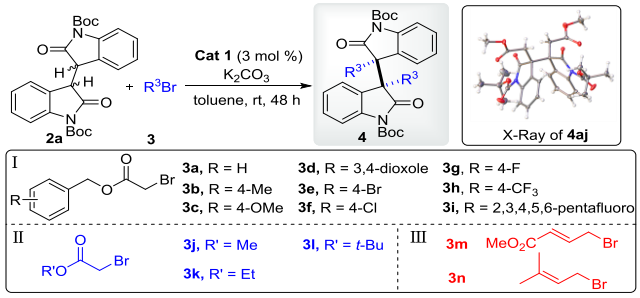
Table 1. Optimization of homo-dialkylation conditions[a]



entry	Cat.	ee (%)[b]	yield (%)[c]	dr[c]
1	**Cat 1**	93	74	12.6:1
2	**Cat 2**	86	61	6.4:1
3	**Cat 3**	78	15	1.5:1
4	**Cat 4**	86	21	1.9:1
5	**Cat 5**	91	30	3.0:1
6	**Cat 6**	-6	26	0.5:1

[a]Reactions were conducted with **2a** (0.0646 mmol, 1 equiv), **3a** (4 equiv), catalyst (3 mol%), DMSO (20 μL) and K_2CO_3 (6 equiv) in 3 mL toluene. [b]Determined by chiral HPLC. [c]Determined by ^{1}HNMR.

Table 2. Investigation of electrophiles for homo-dialkylation[a]

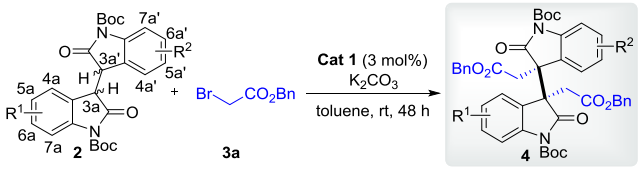


entry	R^3Br (**3**)	product (**4**)[b]	ee (%)[c]	yield (%)[d]	dr[e]
1	**3a**	**4aa**	92	70	12:1
2	**3b**	**4ab**	95	63	12.4:1
3	**3c**	**4ac**	90	66	9.5:1
4	**3d**	**4ad**	93	64	11.3:1
5	**3e**	**4ae**	93	69	11.5:1
6	**3f**	**4af**	91	85	12.5:1
7	**3g**	**4ag**	94	89	11.9:1
8	**3h**	**4ah**	89	86	12.8:1
9	**3i**	**4ai**	88	73	11:1
10	**3j**	**4aj**	95	62[e]	11.9:1
11[f]	**3k**	**4ak**	90	81	8.9:1
12	**3l**	**4al**	-	ND[g]	-
13[h]	**3m**	**4am**	90	82	2.1:1
14[i]	**3n**	**4an**	46	89	> 20:1

[a]Unless otherwise specified, reactions were conducted with **2a** (0.0646 mmol, 1 equiv), **3** (4 equiv), **Cat 1** (3 mol%), DMSO (20 μL), K_2CO_3 (6 equiv) in 3 mL toluene. [b]Absolute configurations were assigned by X-ray of **4aj**. [c]Determined by chiral HPLC. [d]Isolated yields. [e]Determined by ^{1}HNMR. [f]Reacted for 10 days. [g]Not detected. [h]Reacted for 24 h without DMSO. [i]Reacted for 48 h without DMSO.

Group **III**: allylic bromides **3m** and **3n**) worked well to generate the expected homo-dialkylation products **4aa**–**4an** with satisfactory results in most cases (entries 1–14). In Group **I**, all electrophiles **3a**–**i** (entries 1–9) could react smoothly to give high enantioselectivity (88–95% ee) as well as good chemical yield (63–89%). Notably, the electronic properties of substituents at the benzyl moieties of these electrophiles showed certain influences on reaction outcomes, with the 4-F-benzyl ester **3g** giving the best result (entry 7). For Group **II** (entries 10–12), a steric influence of the alkyls on reaction efficiency was evident. For example, the small methyl ester **3j** could react to provide **4aj** in only 2 days with excellent stereoselectivity (entry 10), whereas a bulkier ethyl ester **3k** needed a much longer reaction time of 10 days (entry 11). Moreover, when the much bulkier *t*-butyl ester **3l** was applied to this system, the desired product **4al** was undetectable (entry 12). The allylic electrophiles **3m** and **3n** in Group **III** were also viable for this reaction, however providing the results in inconformity. **3m** reacted to give high ee and yield **(**entry 13), while **3n** generated high dr and yield (entry 14).

Table 3. Investigation of bisoxindoles for homo-dialkylation[a]



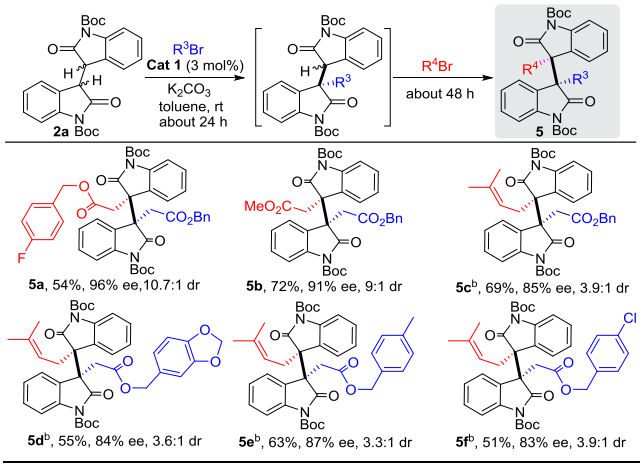
entry	R^1	R^2	product	ee (%)[b]	Y (%)[c]	dr[d]
1	C_{7a}-Me	H	**4ba**	99	41	> 20:1
2	C_{7a}-Br	H	**4ca**	95	70	> 20:1
3	C_{7a}-Cl	H	**4da**	99	82	> 20:1
4	C_{7a}-F	H	**4ea**	97	85	12.9:1
5	C_{7a}-CF_3	H	**4fa**	96	60	> 20:1
6	C_{6a}-OMe	H	**4ga**	89	57	5.6:1
7	C_{6a}-Br	H	**4ha**	98	58	15.6:1
8	C_{6a}-Cl	H	**4ia**	97	65	12.6:1
9	C_{6a}-F	H	**4ja**	97	68	12.5:1
10	C_{5a}-OMe	H	**4ka**	87	47	8.6:1
11	C_{5a}-Me	H	**4la**	90	52	8.7:1
12	C_{5a}-Cl	H	**4ma**	94	58	12.9:1
13	C_{5a}-Me C_{7a}-Me	H	**4na**	96	46	16.9:1
14	C_{5a}-Me	$C_{5a'}$-Cl	**4oa**	92	53	> 20:1
15	C_{7a}-Me	$C_{5a'}$-Cl	**4pa**	98	68	9.6:1
16	C_{5a}-Me	$C_{5a'}$-Me	**4qa**	95	67	> 20:1
17	C_{6a}-Cl	$C_{6a'}$-Cl	**4ra**	92	85	7.1:1
18[e]	C_{5a}-OMe	$C_{5a'}$-OMe	**4sa**	92	78	18:1

[a]Unless otherwise specified, reactions were conducted with **2** (0.0646 mmol, 1 equiv), **3a** (4 equiv), **Cat 1** (3 mol%), K_2CO_3 (6 equiv) in 3 mL toluene. [b]Determined by chiral HPLC. [c]Isolated yields. [d]Determined by ^{1}HNMR. [e]With DMSO (20 μL).

Next, a wide range of bisoxindoles **2** with various mono- and di- substituents on aromatic rings were investigated using **3a** as the electrophile. As summarized in Table 3, a wide range of substrates tolerated to this reaction with high enantioselectivity and good to high yields. For mono-substitution at C_{5a}, C_{6a} or C_{7a}, the EWG′s (electron-withdrawing group) substitutions (entries 2–5, 7–9, and 12) were generally favorable and gave the excellent results (58–85% yield, 94–99% ee, 12.5:1 to > 20:1 dr) over the EDG′s (electron-withdonating group) substitutions (41–57% yield, 87–99% ee, 5.6:1 to > 20:1 dr, entries 1, 6, 10, and 11). However, a C_{4a}-Cl substituted substrate could not give the desired product but only resulted in a complex mixture, probably due to its steric shielding over the reaction sites (C_{3a} or $C_{3a'}$). In the case of disub-

stituted substrates (entries 13–18), both unsymmetrical (entries 13–15) and symmetrical (entries 16–18**)** disubstitutions were effective in this reaction, affording excellent enantioselectivities (92–98% ee), good to high diastereoselectivities (7.1:1 to > 20:1 dr) as well as moderate to good yields (46–85%). Similar to the mono-substitutions, the electronic properties of disubstitutions also had a significant influence on the reaction outcome. For example, the dichloride substituted substrate reacted quickly to produce the corresponding product **4ra** with a high yield of 85% and 92% ee (entry 17), while the dimethoxy substituted substrate produced a poor result (33% yield, 98% ee, and > 20:1 dr) and required further improvement by the addition of DMSO as a polar co-solvent to generate **4sa** with better efficiency (78% yield, 92% ee, 18:1 dr, entry 18). Importantly, the products **4ca** and **4da** with Br and Cl at C_{7a} were valuable for the synthesis of more complex trimeric HPI alkaloids via C-C coupling and further transformations.[1,4]

Table 4. Investigation of hetero-dialkylation of 2a[a]

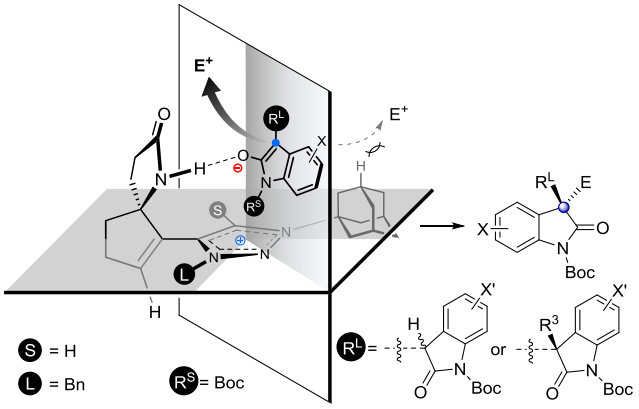


[a]Unless otherwise specified, reactions were conducted in one-pot: **2a** (0.0646 mmol, 1 equiv), R^3Br (1 equiv), **Cat 1** (3 mol%), K_2CO_3 (2 equiv) in 1 mL toluene, then, R^4Br (3 equiv), DMSO (20 μL), and K_2CO_3 (4 equiv), toluene (2 mL); Isolated yields; ee determined by chiral HPLC; dr determined by ^{1}HNMR. [b]2 equiv R^4Br and 1 equiv K_2CO_3 without DMSO in the second step.

Having accomplished the homo-dialkylation of bisoxindoles, we then investigated the more challenging one-pot hetero approach with two different electrophiles R^3Br and R^4Br (Table 4). Initially we tested the mono-alkylation of **2a** with only one equivalent of **3a** under the catalysis of **Cat 1** (3 mol%). The chemoselectivity was satisfactory and the mono-alkylation product was observed in about 85% yield with no dialkylation product detected. In light of this observation, we then added **3g** to the reaction system after **2a** disappeared. This resulted in the generation of the desired hetero-dialkylation product **5a** in 54% yield, 96% ee and 10.7:1 dr. Encouraged by this outcome, more hetero dialkylation reactions were conducted using different electrophiles R^3Br and R^4Br, all producing the expected hetero-products **5b**–**f** with acceptable results. In particular, **5c**–**f** could be used as key intermediates in the synthesis of complex hetero HPI alkaloids because of the distinct reactivity between R^3 and R^4 which facilitates late-stage transformation.[1,4]

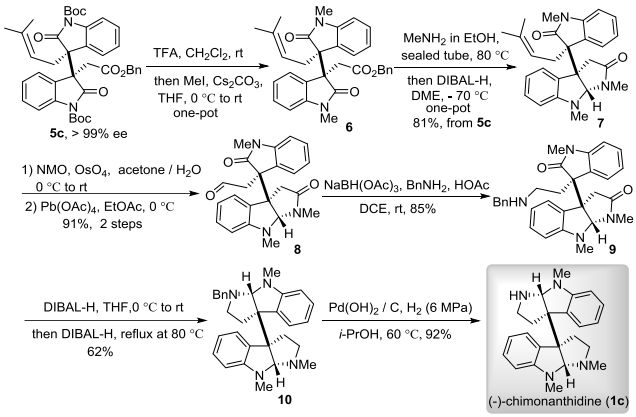
Despite the well-established alkylation sequence for triazolium catalysis, the stereo-control of this reaction process needs to be further considered, and thus a nucleophilic attack model (Scheme 2) for both mono- and di-alkylations was suggested, according to the observed stereochemistry.[13] Since **Cat 6** without the amide

Scheme 2. Rationale for stereo-control



N-H moiety showed poor stereoselectivity, both a hydrogen bonding and an ion-pairing interaction between **Cat 1** and the enolate might exist during each alkylation steps. Presumably due to the steric hindrance of the adamantyl group, nucleophilic attack of the intermediate toward the electrophile from the back face was unfavorable, thus leading to the formation of the major (*S*, *S*)-dialkylated product.

Scheme 3. Total synthesis of (–)-chimonanthidine (1c)



To verify the efficient utility of catalytic asymmetric dialkylation strategies established above, we carried out a formal synthesis of (–)-folicanthine (**1a**)[14] and the first asymmetric total synthesis of (–)-chimonanthidine (**1c**) (Scheme 3).[15] A major challenge in the synthesis of **1c** was to selectively protect only one *N*-H with a methyl group at two pyrrolidine rings, which could be easily addressed using the hetero-dialkylation product **5c** (prepared in gram-scale reaction[13] and at > 99% enantio-purity after recrystallization) as the key intermediate. Accordingly, the key building block **7** was efficiently obtained from **5c** in a one-column purification with an 81% overall yield, in which a regioselective reductive amination/cyclization of oxindole moiety was achieved. The subsequent oxidative cleavage of the C=C bond of olefin **7** followed by reductive benzylamination yielded product **9**. Another reductive amination/cyclization of **9** formed the second pyrrolidine ring of **10**. Selective removal of the benzyl protecting group of **10** by $Pd(OH)_2$/C-catalyzed hydrogenolysis completed the asymmetric total synthesis of (–)-**1c**.

In conclusion, we have successfully developed the SPA-triazolium cation catalyzed asymmetric homo- and hetero-dialkylation of bisoxindoles. These reactions allowed the direct construction of the challenging vicinal all-carbon quaternary stereocenters in high efficiencies (up to 82% yield, 99% ee, > 20:1 dr). To our knowledge, this transformation is so far the most efficient approach for assembling this congested unit. Additionally,

product **5c** has been readily applied to the first asymmetric total synthesis of (–)-chimonanthidine (**1c**). The diverse synthesis of other HPI alkaloids is ongoing in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at http://pubs.acs.org.

Experimental details (PDF)
X-ray data for compound **Cat 4** (CIF)
X-ray data for compound **4aj** (CIF)

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Notes

The authors declare no competing financial interests.

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